

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Decl.
4/24/02

In re Application of:
CHATFIELD
Serial No. 09/527,919
Filed: March 17, 2000
For: HEPATITIS B VIRUS
POLYPEPTIDES

DECLARATION

The Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I, Mark Page, declare as follows:

1. I am currently Senior Director of Immunology of Apovia Inc, a company which is located in both San Diego, California and Munich, Germany. Before that, I was Head of Celltech Medeva's Vaccine Research Unit in London, England. A copy of my curriculum vitae is attached. The work described in the patent application was carried out in Celltech Medeva's Vaccine Research Unit.
2. I have been asked to comment on the argument made by the Examiner in the "Official Action" of 18 October 2001 that the invention claimed in the patent application was obvious over Mimms et al (European Patent Application EP-A- 389983), Khan et al (International Patent Application WO 94/03615) and Shi et al (Vaccine 1995, Vol. 13, pp. 933-937). I have read the patent application in question, the Official Action and the references cited by the Examiner.
3. The invention that is the subject of the application in question relates to fusion

polypeptides comprising tetanus toxin fragment C (or a fragment thereof) fused to pre-S sequence of hepatitis B virus. The idea is that the tetanus toxin fragment C acts as a "carrier" for the pre-S sequence and promotes the induction of an immune response against the pre-S sequence.

4. At the time the invention was made, a very large number of carriers proteins were known to scientists working in the field. For example, the following had been used as carriers: keyhole limpet hemocyanin (KLH), gelatin, albumin, ovalbumin, casein, bovine gammaglobulin (BGG), erythrocytes, lipopolysaccharide (LPS), carboxymethyl cellulose, poly-DL-lysine, mycobacterial heat shock proteins, micelles, liposomes, virosomes, immune stimulating complexes (ISCOMs), proteosomes, β -galactosidase, bacterial outer membrane and periplasmic proteins, hepatitis B core antigen, hepatitis B surface antigen, retroviral Gag proteins, phage coat proteins, retrotransposon Ty protein p1, the B subunit of heat labile toxin of *E.coli* and the B subunit of cholera toxin.

5. The number of antigenic sequences which could potentially be linked to each of these carriers was even greater than the number of potential carriers. The international patent application cited by the Examiner, WO 94/03615 of Khan et al, itself lists a very large number of antigenic sequences in the passage bridging pages 5 and 6. It lists antigenic sequences of HIV such as HIV-1 and HIV-2, e.g. the CD4 receptor binding site from HIV; hepatitis A virus; hepatitis B virus; human rhinovirus such as type 2 or type 14 rhinovirus; herpes simplex virus; poliovirus type 2 and 3; foot-and-mouth disease virus (FMDV); rabies virus; rotavirus; influenza virus; coxsackie virus; human papiloma virus (HPV); such as HPV type 16 and the E7 protein thereof and fragments of the E7 protein; simian immunodeficiency virus (SIV); *Bordetella pertussis* such as the P69 protein and filamentous hemagglutinin (FHA); *Vibrio cholerae*; *Bacillus anthracis*; *E.coli* such as the B subunit of heat labile toxin (LTB), the K88 antigens and enterotoxigenic antigens; the cell surface antigen CD4; *Schistosoma mansoni* such as p28 glutathione S-transferase antigens (p28 antigens); and flukes, mycoplasma, roundworms, tapeworms, *Chlamydia trachomatis*, and malaria parasites.

6. Thus, there were a vast number of combinations of carrier protein and antigenic sequence that could in theory have been put together by a scientist working in the field. I am not aware of any particular reason why a scientist would have chosen to put together fragment C and pre-S of hepatitis B out of all the other possible combinations that could potentially have been put together. The references cited by the Examiner, EP-A-389983 of Mimms, WO 94/03615 of Khan et al and Shi et al, were not references which were high profile references in the field and I cannot see any particular reason why a scientist would have put the three of them together.

7. It was far from obvious that the combination of fragment C and pre-S sequence would induce a good antibody response against the pre-S sequence. The design of immunogens is an empirical art. It is difficult or impossible to predict in advance whether a particular polypeptide will induce a good immune response such as an antibody response. In order to find out whether a polypeptide will induce such a response, it is necessary to make the polypeptide and test it in animal models. It is generally not possible to predict in advance with any reasonable degree of certainty whether a given polypeptide will work or not.

8. The unpredictability of the art manifests itself in the Shi et al paper cited by the Examiner. Shi et al describes fusion of cholera toxin B subunit (CTB) to pre-S2 epitope. The fusion protein produced an extremely low antibody titre against the pre-S2 region. This is clear from, for example, Figure 7 on page 936 of Shi et al. The Figure shows that the peak antibody titre against CTB was about 5000, whereas the peak titre against pre-S2 was only about 140. A different scale had to be used for the anti-pre-S2 titre compared to that for the anti-CTB titre in order to present the anti-pre-S2 titre on the graph! The peak anti-pre-S2 titre was about 35 times less than the peak anti-CTB titre.


9. Thus, Shi et al suggested that the invention claimed in the patent application was not likely to be successful. The cholera toxin B subunit used as the carrier in Shi et al is similar to fragment C of tetanus toxin in that both are both are parts of bacterial toxins that are used as carriers because they are potent immunogens. The fact that cholera toxin B subunit did not work would have suggested that other bacterial toxins such as fragment C may not work.

10. The discussion section of Shi et al on pages 936-937 puts forward various possible reasons for the extremely low titre of pre-S2 antibody but does not reach any firm conclusions. It was apparently not clear to the authors of Shi et al why the titre was so low.

11. In contrast to Shi et al, the data in the patent application in question show that a good antibody response can be induced against pre-S by the fusion proteins that are the subject of the application. For example, the results presented in Figure 3B of the application show that, seven days after a booster dose, the fusion proteins induce a good antibody titre against a pre-S1 peptide. The titre is of the same order of magnitude as that against the fragment C component of the proteins (see Figure 2B). These results would not have been expected from a reading of Shi et al and the other references mentioned by the Examiner.

12. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardise the validity of this Declaration, the patent application, or any patents issuing thereon.

Declared this 9th day of April 2002



Mark Page, PhD.

CURRICULUM VITAE

PERSONAL DETAILS

Name: Mark Page
Date of birth: 4th November 1957
Nationality: British
Marital status: Married, 2 children

APPOINTMENTS

August 2001-date Senior Director of Immunology, Apovia Inc., 11125 Flintkote Ave., San Diego, CA 92121 and Fraunhoferstr. 10, 82152 Martinsried, Munich, Germany

March 2001 – July 2001 Part-time consultancy work.

March 1997 – Feb. 2001 Head of Vaccine Research Unit, Celltech-Medeva, Dept. Biochemistry, Imperial College, Exhibition Road, London SW7 2AY

Dec. 1995 - March 1997 Senior Scientist, Vaccine Research Unit, Medeva, Dept. Biochemistry, Imperial College, Exhibition Road, London SW7 2AY

Sept. 1988 - Nov. 1995 Scientist, Division of Immunobiology, National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Hertfordshire.

Sept. 1985 - Aug. 1988 ARC Post Doctoral Research Fellow, Department of Anatomy, University College London, Gower Street, London.

Oct. 1983 - Sept. 1985 MRC Post Doctoral Research Fellow, Department of Anatomy, St. George's Hospital Medical School, Tooting, London.

ACADEMIC HISTORY

Sept. 1979 - Sept. 1983 Department of Zoology, University College, Swansea, Wales.
Ph.D.: Immunology of Cyclostomes

Sept. 1976 - July 1979

University College, Swansea, Wales.
Degree: B.Sc. (Hons) Zoology (Upper second)

1969 - 1976

Barton Peveril Grammar School, Eastleigh, Hants.
A levels: Biology, Chemistry and Physics

MANAGERIAL / COMMUNICATION / ADMINISTRATION SKILLS

Management of and responsibility for all immunology projects at Apovia. Management of staff at Apovia's Munich operations. Responsibility for strategic operation of Apovia's product pipeline reporting to CEO.

Management of research laboratory (resources, budget (£850k pa), scientific activities) and direction of its activities (10 staff). Generation and selection of recombinant DNA vaccine candidates for phase I clinical trial evaluation. Antigen and epitope discovery using animal and in vitro human sample models.

Input and advise on company policy and strategic decisions for vaccine development through positions on management executive committee and project teams.

Interaction with external academic and industrial groups at senior level and strategic decision making on potential collaborations and licensing opportunities. Maintenance of collaborations with third parties through regular meetings to decide on direction and policy.

Presentation of Medeva development pipeline to analysts in London and New York.

Publication of results in scientific journals.

Filing of patents from research data. Interaction with patent attorneys.

Writing business plan for start up company (potential spin out from Celltech-Medeva). Liaising with Venture Capitalists to raise seed funding for start up.

LICENSING SKILLS

Provision of data reports generated from scientific analyses carried out by the Unit I manage and for inclusion in a license application for a new hepatitis B vaccine (Hepacare) that was subsequently approved by the EMEA (March 2000). Full review of the above license application before submission.

SCIENTIFIC SKILLS

Cell Biology:	Monoclonal antibody production, aseptic techniques, handling category II/III pathogens, virus cultures, virus neutralization assays, electron microscopy, cryostat sectioning, histology, histochemistry.
Biochemistry:	Protein purification and identification, electrophoresis, isoelectric focusing, chromatography including HPLC and FPLC, peptide synthesis.
Immunochemistry:	Immunofluorescence, RIPA, immunoblotting, ELISA, IRMA, RIA, immunohistochemistry, immunocytochemistry, antibody preparation and purification, antibody affinity chromatography.
Immunology:	T cell proliferation assay, cytotoxic T cell assay, antibody subclass determination.
Molecular Biology:	Gene cloning, PCR, RNA/DNA sequencing, recombinant DNA protein expression and purification.

REGULATORY AFFAIRS / QUALITY ASSURANCE EXPERIENCE

Consultant for both UK Medicines Control Agency and European Community National Agencies on licence applications for immunoglobulins and monoclonal antibodies when at NIBSC.

Responsibility for control of all UK licensed immunoglobulin products and issue of batch release certificates when at NIBSC.

Quality Co-ordinator, Study Director and Audit Officer responsibilities for implementing, operating and maintaining a Quality System at NIBSC in accordance with the NAMAS Accreditation Standard (BS7501; EN45001).

Certified Internal Quality Auditor for auditing to ISO 9000.

OTHER

Clean driving licence, computer literate (MicroSoft Office Suite, Outlook).

REFEREES

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PUBLICATIONS

1. Page, M. & Rowley, A.F. (1982). A morphological study of pharyngeal lymphoid accumulations in larval lampreys. *Dev. Comp. Immunol. Suppl.* 2, 35-40.
2. Page, M. & Rowley, A.F. (1983). A cytochemical, light and electron microscopical study of the leucocytes of the adult river lamprey, *Lampetra fluviatilis* (L. Gray). *J. Fish. Biol.* 22, 503-517.
3. Page, M. & Rowley, A.F. (1984). The reticulo-endothelial system of the adult river lamprey, *Lampetra fluviatilis* (L): the fate of intravascularly injected colloidal carbon. *J. Fish Dis.* 7, 339-353.
4. Rowley, A.F. & Page, M. (1985). Ultrastructural, cytochemical and functional studies on the eosinophilic granulocytes of larval lampreys. *Cell Tiss. Res.* 240, 705-709.
5. Rowley, A.F. & Page, M. (1985). Lamprey melano-macrophages: structure and function. *In: Fish Immunology* (eds. M.J. Manning & M.F. Tatner), pp.273-284. London: Academic Press.
6. Rowley, A.F., Mainwaring, G., Hunt, T.C. & Page, M. (1988). Fish. *In: Vertebrate Blood Cells* (eds. A.F. Rowley & N.A. Ratcliffe). Cambridge: Cambridge University Press.

7. Page, M., Hogg, J. & Ashhurst, D.E. (1986). The effects of mechanical stability on the macromolecules of the connective tissue matrices produced during fracture healing. I The collagens. *Histochem. J.* 18, 251-265.
8. Page, M. & Ashhurst, D.E. (1986). The distribution of types I, II, III and V collagens in healing fractures of the rabbit tibia. *In: Cell Mediated Calcification and Matrix Vesicles* (ed. Y.S. Ali). Pp. 161-166. Amsterdam: Elsevier.
9. Page, M. & Ashhurst, D.E. (1987). The effects of mechanical stability on the macromolecules of the connective tissue matrices produced during fracture healing. II. The glycosaminoglycans. *Histochem. J.* 19, 39-61.
10. Ashhurst, D.E. & Page, M. (1987). Collagens and glycosaminoglycans associated with fracture healing. *In: Current Advances in Skeletogenesis* (eds. S. Hurwitz & J. Sela), vol. 3, p.132. Jerusalem: Heiliger Publishing House.
11. Page, M. (1988). Changing patterns of cytokeratin and vimentin in the early chick embryo. *Development* 105, 97-107.
12. Loveless, W., Bellairs, R., Thorpe, S.J., Page, M. & Feizi, T. (1990). Developmental patterning of the carbohydrate antigen FC10.2 during early embryogenesis in the chick. *Development* 108, 97-106.
13. Almond, N., Page, M., Kills, K., Jenkins, A., Ling, C., Thorpe, R. & Kitchin, P. (1990). The production and purification of PCR derived recombinant simian immunodeficiency virus p27 gag protein: its use in detecting serological and T cell responses in macaques. *J. Virol. Methods* 28, 321-326.
14. Kitchin, P.A., Cranage, M.P., Almond, N., Barnard, A., Baskerville, A., Corcoran, T., Fromolt, C., Greenway, P., Grief, C., Jenkins, A., Kent, K., Ling, C., Mahon, B., Mills, K., Page, M., Silvera, P., Szotoryi, Z., Taffs, F. & Stott, E.J. (1990). Titration of SIV MAC 251 (32H isolate) in cynomolgus macaques for use as a challenge in vaccination studies. *In: Animal models in AIDS* (eds. H. Schellekens & M.C. Horzine), p.p.115-129. Amsterdam: Elsevier Science Publishers.
15. Page, M. & Thorpe, R. (1990). Controlling for false positive antisera in human immunodeficiency virus immunoblotting. *J. Infect. Dis.* 162, 178.
16. Stott, E.J., Chan, W.L., Mills, K.H.G., Page, M., Taffs, F., Granage, M., Greenway, P. & Kitchin, P. (1991). Preliminary report: Protection of cynomolgus macaques against simian immunodeficiency virus by a whole fixed infected cell vaccine. *Lancet* 336, 1536-1541.
17. Page, M., Patel, V., Dilger, P., Ling, C. & Thorpe, R. (1991). Antisera raised against recombinant soluble CD4s can have reactivity to recombinant HIV-1 envelope glycoproteins. *AIDS* 5, 321-324.
18. Page, M., Mills, K.H.G., Schild, G.C., Ling, C., Patel, V., McKnight, A., Barnard, A.L., Dilger, P. & Thorpe, R. (1991). Studies on the immunogenicity of CHO cell-derived recombinant gp120 (HIV1-IIIB) envelope glycoproteins. *Vaccine* 9, 47-52.
19. Stott, E.J., Kitchin, P.A., Page, M., Flanagan, B., Taffs, L.F., Chan, W.L., Mills, K.H.G., Silvera, P. & Rodgers, A. (1991). Anti-cell antibody in macaques. *Nature* 353, 393.
20. D'Souza, P., Durda, P., Hanson, C.V., Milman, G. and Collaborating Investigators (1991). Evaluation of monoclonal antibodies to HIV-1 by neutralization and serological assays: an international collaboration. *AIDS* 5, 1061-1070.
21. Mills, K.H.G., Barnard, A.L., Williams, M., Page, M. *et al.* (1991). Vaccine-induced CD4⁺ T cells against the simian immunodeficiency virus gag protein: Epitope specificity and relevance to protective immunity. *J. Immunol.* 147, 3560-3567.
22. Stott, J., Cranage, M., Kitchin, P., Farrar, G., Taffs, F., Ashworth, E., Page, M., Chan, L., Baskerville, A., Greenaway, P. & Mills, K. (1991). Vaccination against simian-

- immunodeficiency virus infection of macaques. *In: Retroviruses of human AIDS and related animal diseases. Sixieme colloque des cent gardes 1991* (eds. M. Girard & L. Valette), p.p. 261-265. Pasteur Merieux.
23. Thorpe, R., Brasher, M., Tarelli, E., Dilger, P. & Page, M. (1992). Laboratory evaluation of IVIG preparations. *In: Clinical Applications of Intravenous Immunoglobulin Therapy* (ed. Peng Lee Yap), pp. 253-262. Churchill Livingstone.
 24. Page, M., Vella, C., Corcoran, T., Dilger, P., Ling, C., Heath, A. & Thorpe, R. (1992). Restriction of serum antibody reactivity to the V3 neutralising domain of HIV gp120 with progression to AIDS. *AIDS* 6, 441-446.
 25. Cranage, M., Stott, J., Mills, K., Ashworth, T., Taffs, F., Farrar, G., Chan, W.L., Dennis, M., Putkonen, P., Biberfeld, G., Murphey-Corb, M., Baskerville, A., Page, M., Kitchin, P. & Greenaway, P. (1992). Vaccine studies with the 32H reisolate of SIV mac251: an overview. *AIDS Res. Hum. Retrovir.* 8, 1479-1481.
 26. Mills, K.H.G., Page, M., Chan, W.L., Kitchin, P., Stott, E.J., Taffs, F., Jones, W. *et al.* (1992). Protection against SIV infection in macaques by immunization with inactivated virus from the BK28 molecular clone but not with KB28-derived recombinant env and gag proteins. *J. Med. Primatol.* 21, 50-58.
 27. D'Souza, M.P., Kent, K.A., Thiriart, C., Collignon, C., Milman, G. & Collaborating Investigators. (1993). International Collaboration comparing neutralization and binding assays for monoclonal antibodies to simian immunodeficiency virus. *AIDS Res. Hum. Retr.* 5, 415-422.
 28. McKeating, J.A., Shotten, C., Cordell, J., Graham, S., Balfe, P., Sullivan, N., Charles, M., Page, M., Bolmstedt, A., Olofsson, S., Kayman, S.C., Wu, Z., Pinter, A., Dean, C., Sodroski, J. & Weiss, R.A. (1993). Characterisation of neutralising monoclonal antibodies to linear and conformation-dependent epitopes within the first and second variable domains of human immunodeficiency virus type 1 gp120. *J. Virol.* 67, 4932-4944.
 29. Mills, K.H.G., Jones, W.C., Mahon, B.P., Katrak, K., Taffs, F., Stott, E.J. & Page, M. (1993). Cellular and humoral immune responses to poliovirus and tetanus following primary immunization of SIV-infected macaques. *In: Animal Models of HIV and other Retroviral Infections* (eds. P. Racz, N.L. Letvin & J.C. Gluckman) p.p.75-85. Basel: Karger.
 30. Kitchin, P., Mills, K., Page, M., Taffs, F., Chan, W.L., Cranage, M., Farrar, G., Greenaway, P. & Stott, E.J. (1993). Vaccination of macaques against SIV infection and the significance of host (C8166) cell components. *In: Vaccines '93*. New York: Cold Spring Harbor Laboratory Press, Cold Spring Harbor.
 31. Stott, E.J., Almone, N., Kent, K.A., Chan, W.L., Cranage, M.P., Kitchin, P.A., Mills, K.H.G., Page, M. & Rud, E. (1993). Animal Models in the Development of AIDS Vaccines. *In: Retroviruses of Human AIDS and related Animal Diseases. Huitieme Colloques des Cent Gardes 1993* (eds. M. Girard & L. Valette), p.p. 131-137. Pasteur Merieux.
 32. Mills, K.H., Page, M., Kitchin, P., Chan, L., Jones, W., Silvera, P., Corcoran, T., Flangan, B., Ling, C., Thiriart, C. *et al.* (1993). Immunisation of macaques with SIV env recombinants: specificity of T cell and antibody responses and evaluation of protective efficacy. *J. Med. Primatol.* 22, 104-109.
 33. Page, M. (1994). Viral Safety. *In: Immunochemistry Labfax* (eds. R. Thorpe & M. Kerr). Bios Scientific Publishers.

34. Brokstad, K.A., Page, M., Nyland, H. & Haaheim, L.R. (1994). Auto antibodies to myelin basic protein are not present in the serum and cerebrospinal fluid of multiple sclerosis patients. *Acta Neurol. Scand.* 89, 407-411.
35. Brokstad, K.A., Kalland, K.H., Pagae, M., Nyland, H. & Haaheim, L. (1994). Serum antibodies in MS patients do not recognize HTLV-I, HIV-1, HIV-2 and SIV. *Acta Path. Microbiol. Immunol. Scand.* 102, 514-520.
36. D'Souza, M.P., Geyer, S.J., Hanson, C.V., Hendry, R.M., Milman, G. & Collaborating Investigators (1994). Evaluation of monoclonal antibodies to HIV-1 envelope by neutralisation and binding assays: an international collaboration. *AIDS* 8, 169-181.
37. Kent, K.A., Kitchin, P., Mills, K.H.G., Page, M., Taffs, F., Corcoran, T., Silvera, P., Flanagan, B., Powell, C., Rose, J., Ling, C., Aubertin, A.M. & Stott, E.J. (1994). Passive immunization of cynomolgus macaques with immune sera or a pool of neutralizing monoclonal antibodies failed to protect against challenge with SIVmac251. *AIDS Res. Hum. Retr.* 10, 189-194.
38. Page, M., Baines, M. & Thorpe, R (1994). Preparation of purified immunoglobulin G (IgG). In: *Methods in Molecular Biology. Vol. 32: Basic Protein and Peptide Protocols* (ed. J. Walker), p.p. 407-432. New Jersey: Humana Press.
39. Page, M., Ling, C., Dilger, P., Bentley, M., Forsey, T., Longstaff, C. & Thorpe, R. (1995). Fragmentation of therapeutic human immunoglobulin preparations. *Vox. Sang.* 69, 183-194.
40. Kotitschke, R., Lang, H. & Page, M. (1995). IgG subclass distribution in intravenous immunoglobulin products: determination of reproducibility of a method of IgG subclass determination. Ring Study of the "Plasma Blood Components" Section of the German Society of Transfusion Medicine and Immunohematology. *Infusionsther Transfusionsmed.* 22, 360-363.
41. Page, M. & Thorpe, R. 1996. Purification of IgG by precipitation with sodium sulfate or ammonium sulfate. In: *The Protein Protocols Handbook*. Ed. Walker, J.M. Humana Press Inc. N.J. pp.723.
42. Page, M. & Thorpe, R. 1996. Purification of IgG using DEAE-Sepharose chromatography. In: *The Protein Protocols Handbook*. Ed. Walker, J.M. Humana Press Inc. N.J. pp.725.
43. Page, M. & Thorpe, R. 1996. Purification of IgG using Ion-exchange HPLC/FPLC. In: *The Protein Protocols Handbook*. Ed. Walker, J.M. Humana Press Inc. N.J. pp.727.
44. Page, M. & Thorpe, R. 1996. Purification of IgG by precipitation with polyethylene glycol (PEG). In: *The Protein Protocols Handbook*. Ed. Walker, J.M. Humana Press Inc. N.J. pp.731.
45. Page, M. and Thorpe, R. 1996. Purification of IgG using protein A or protein G. In: *The Protein Protocols Handbook*. Ed. Walker, J.M. Humana Press Inc. N.J. pp.733.
46. Page, M. & Thorpe, R. 1996. Purification of IgG using gel-filtration chromatography. In: *The Protein Protocols Handbook*. Ed. Walker, J.M. Humana Press Inc. N.J. pp.735.
47. Page, M. & Thorpe, R. 1996. Purification of IgG using affinity chromatography on antigen-ligand columns. In: *The Protein Protocols Handbook*. Ed. Walker, J.M. Humana Press Inc. N.J. pp.739.
48. Page, M. & Thorpe, R. 1996. Purification of IgG using thiophilic chromatography. In: *The Protein Protocols Handbook*. Ed. Walker, J.M. Humana Press Inc. N.J. pp.743.
49. Page, M. & Thorpe, R. 1996. Analysis of IgG fractions by electrophoresis. In: *The Protein Protocols Handbook*. Ed. Walker, J.M. Humana Press Inc. N.J. pp.745.

50. Ferguson, M., Minor, P.D., Garrett, A.J., Page, M., Thorpe, R. & Barrowcliffe, T. 1996. Testing plasma pools for markers of viral contamination: the UK experience. *Vox Sang* 71, 21-26.
51. Page, M. & Robin Thorpe. 1998. Purification of monoclonal antibodies. In: *Methods in Molecular Biology : Immunochemical protocols*. Ed. Pound, J.D., Humana Press. Totowa, New Jersey, pp. 95-111.
52. Page, M. & Robin Thorpe. 1998. IgG purification. In: *Methods in Molecular Biology : Immunochemical protocols*. Ed. Pound, J.D., Humana Press. Totowa, New Jersey, pp. 113-119.
53. Jones, C.D., Page, M., Bacon, A., Cahill, E., Bentley, M. & Chatfield, S.N. 1998. Characterisation of the T- and B-cell immune response to a new recombinant pre-S1, pre-S2 and SHBs antigen containing hepatitis B vaccine (Hepagene™): evidence for superior anti-SHBs antibody induction in responder mice. *J. Viral Hepatitis* 5, 5-8.
54. Jones, C.D., Page, M., Bacon, A., Cahill, A., Bentley, M. & Chatfield, S.N. 1999. T-cell and antibody response characterisation of a new recombinant pre-S1, pre-S2 and SHBs antigen-containing hepatitis B vaccine; demonstration of superior anti-SHBs antibody induction in responder mice. *Vaccine* 17, 2528-2537.
55. Page, M., Jones, C.C. & Bailey C. (in press). Review: A novel recombinant triple antigen hepatitis B vaccine (Hepacare). *Intervirology*
56. Jung, M.-C., Gruner, N., Zachoval, W., Schraut, W., Gerlach, T., Diepolder, H., Schirren, A., Page, M., Bailey, J., Birtles, E., Whitehead, E., Trojan, J., Zeuzem, S. & Pape, G.R. (submitted). Therapeutic vaccination in chronic hepatitis B: qualitative and quantitative analysis of the hepatitis B virus specific response. *J. Clin. Invest.*

PATENTS

1. Designing immunogens. UK patent application 0007789. (1PCT/GB00/03857).
2. Modification of hepatitis B core antigen. UK patent application 0015308.0
3. A major histocompatibility complex antigen for use as a vaccine against an immunodeficiency virus - W09401130.